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☐ 1. Document ID: CN 1113234 A

L1: Entry 1 of 1 File: DWPI Dec 13, 1995

DERWENT-ACC-NO: 1997-425669
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TITLE: Anthratancitone and its physiological saline synthesis

INVENTOR: CHEN, G; WU, G ; ZHOU, W

PATENT-ASSIGNEE:

ASSIGNEE	CODE
SHANGHAI ORGANIC CHEM INST CHINESE ACAD	SHANN

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ABSTRACTED-PUB-NO: CN 1113234A
BASIC-ABSTRACT:

The present invention relates to a method for preparing compound of the invented chemical constitutional formula (I) and its correspondent free alkali (II). In its constitutional formula A representschlorhydric acid, sulfuric acid, hydrobro mic acid, oxalic acid, maleic acid and perchloric acid, the inorganic and organic acid which can be mathched with (II) to produce acceptable physiological salts, and S represents water solvent. The chemical name of said compound (I) is the solvate of physiological salt of 1,1,2, 2,3-pentahydrogen-9-methyl- 3 (2-methyl-imidazole-1-radical) methyl]-4-oxocarbazole, and is effective 5-HT3 receptor antagonist, and clinically it has the strong therapeutic effect for treating nausea and vomiting due to cis- platinum and noncis-platinum chemotherapy and radiotherapy.

CHOSEN-DRAWING: Dwg.0/0

TITLE-TERMS: PHYSIOLOGICAL SALINE SYNTHESIS

DERWENT-CLASS: B02

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说明书页数: 16　　附图页数:

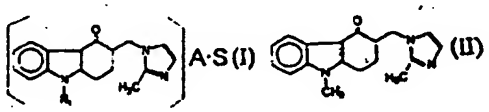
[54]发明名称 恩丹西酮及其生理盐的合成

[57]摘要

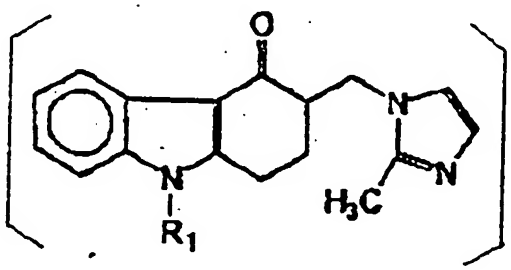
本项发明涉及制备化学结构式（I）的化合物及其相应的游离碱（II）的方法。

结构式中：A 表示盐酸、硫酸、氢溴酸、草酸、马来酸、高氯酸，可以和（II）生成合格生理盐的无机和有机酸；S 表示为水的溶剂。

化合物（I）的化学名是 1，1，2，2，3-五氢-9-甲基-3-[（2-甲基-咪唑-1-基）甲基]-4-氧代咔唑的生理盐的溶剂化物，是有效的 5-HT$_3$ 受体拮抗剂，临床上对由顺铂、非顺铂化疗和放疗引起的恶心、呕吐具有强疗效。



1．通式（Ⅰ）为制备方法:

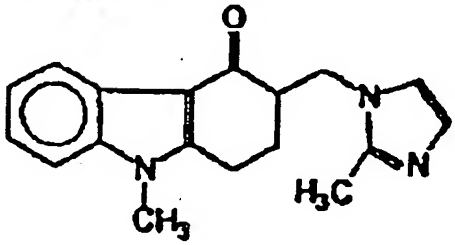


A·S (I)

结构式中: A表示盐酸、硫酸、氢溴酸、草酸、马来酸、有机酸或无机酸; S表示水溶剂; R_1表示 $C_1 \sim C_6$的直链或脂环状烷基;

通式（Ⅰ）的制备方法包括:

（A）通式（Ⅱ）的化合物或其被保护的衍生物或含量高于30%的反应混合物与A之间的固一液界面成盐反应;

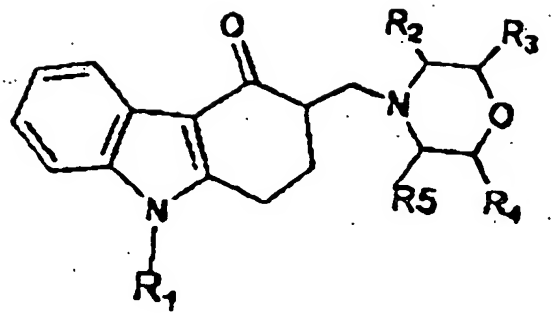


(II)

（B）通式（Ⅱ）的化合物或其被保护的衍生物或含量高于30%的反应混合物与A之间的液一气界面成盐反应.

2．根据权利要求1所述的通式（Ⅱ）的制备方法:

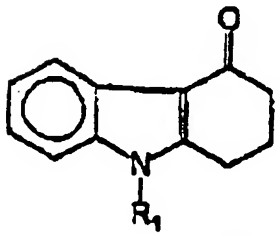
（C）通式（Ⅲ）的化合物和2—甲基咪唑或其他胺交换反应;



(III)

结构式中：R_1表示$C_1 \sim C_6$的直链或脂环状烷基，R_2、R_3、R_4、R_5表示$C_1 \sim C_3$短链正烷基或异烷基或氢原子，R_2、R_3、R_4、R_5可以是相同或不相同的取代基，或无取代基；

（D）化学结构式（IV）化合物和化学结构式（V）或（VI）化合物的酮交换反应：



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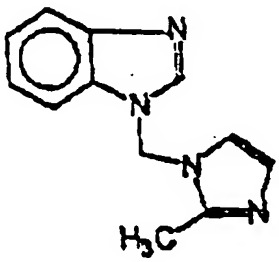
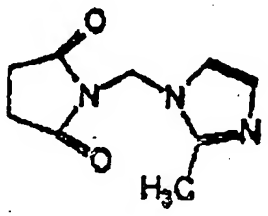


(VI)



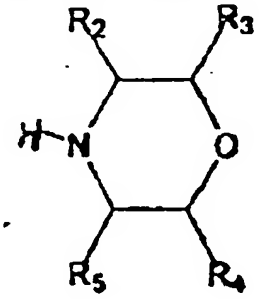
(V)

结构式中：R_1表示$C_1 \sim C_6$的直链或脂环烷基；

（E）化学结构式（IV）化合物，多聚甲醛和2—甲基咪唑的催化缩合反应，反应中所用的固体催化剂是$AgNO_3$、$Cu_2X_2(X=Cl,Br,I)$、$Cu(OAc)_2$、Al_2O_3，Lewis酸或它们的混合式复合催化剂。

3．根据权利要求2所述的制备化学结构式（III）的方法其中包括：

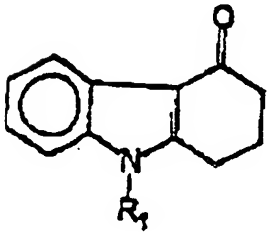
（F）化学结构式（Ⅳ）化合物，多聚甲醛和结构式（Ⅶ）化合物的催化缩合反应，反应中所用的固体催化剂是$AgNO_3$、$Cu_2X_2(X=Cl,Br,I)$、$Cu(OAc)_2$、Al_2O_3 Lewis酸或它们的混合式复合催化剂或盐酸、硫酸、无机酸；



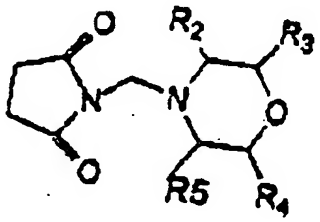
(Ⅶ)

结构式中：R_2、R_3、R_4、R_5表示$C_1\sim C_3$的短链正烷基或异烷基或氢原子；

（G）化学结构式（Ⅳ）化合物和化学结构式（Ⅷ）或（Ⅸ）化合物的酮交换反应；



(Ⅳ)



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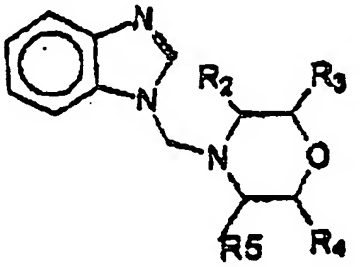


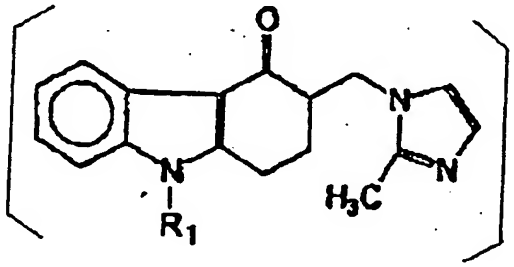
(Ⅸ)

结构式中：R_1表示$C_1\sim C_6$的直链或脂环烷基，R_2、R_3、R_4、R_5表示$C_1\sim C_3$的短链正烷基或异烷基或氢原子。

4. 根据权利要求1至3之一的制备恩丹西酮的众多重要中间体中，特别有用的化合物是1,1,2,2,3-五氢-9-甲基-3-〔（2′-甲基咪唑基-1）-甲基〕-4-氧代咔唑和二氧化硅或离子交换树脂的复合物.

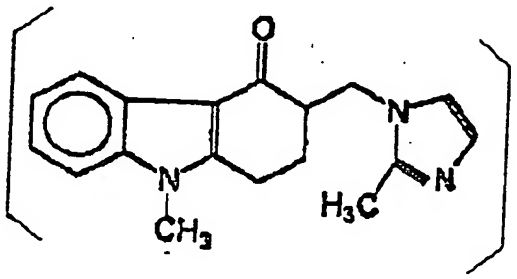
恩丹西酮及其生理盐的合成

本发明涉及医药用的一种有机碱及其合格的生理盐和溶剂化物的制备，该种化合物的化学结构通式用式（Ⅰ）表示：



A·S(I)

结构式中：A表示盐酸、硫酸、氢溴酸、草酸、马来酸、无机酸或有机酸；S表示水溶剂；R_1表示$C_1 \sim C_6$的直链或脂环状烷基．在医药上它的盐酸盐二水化合物（X）习惯商品名为盐酸恩丹西酮．



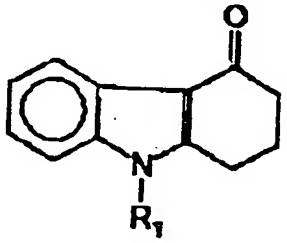
$HCl \cdot 2H_2O$ (X)

化学名为1，1，2，2，3－五氢－9－甲基－3－〔（2′－甲基咪唑－1－基）－甲基〕－4－氧代－咔唑．结构式用（Ⅱ）表示：

地作用于弱酸性离子交换树脂或硅酸G（≤100目）或卡普隆粉或硅藻土或阳性氧化铝载体上和合适浓度的无机酸或有机酸溶液，在固—液界面上发生反应，高选择性地得到通式（Ⅰ）化合物。

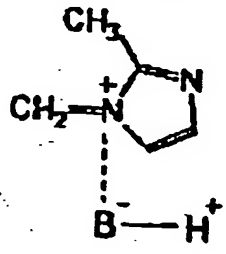
按照本专利提供的制备通式（Ⅰ）化合物的第二种方法（B），通式为（Ⅱ）的化合物或含量大于30%的混合物连续地加入到水—醇溶剂中，同时连续地通入氯化氢等气体，可经连续地获得通式为（Ⅰ）的化合物。

按照本专利提供的制备通式（Ⅱ）的制备方法（E），化学结构式（Ⅳ）化合物是芳香酮类化合物，2-甲基咪唑是芳香胺类化合物，它们在普通的Mannich反应条件下，主要发生胺醛的缩合反应，生成树脂状缩聚物，而且，属芳香酮类的通式（Ⅳ）化合物的

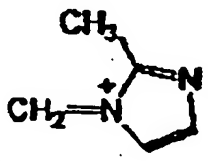


(Ⅳ)

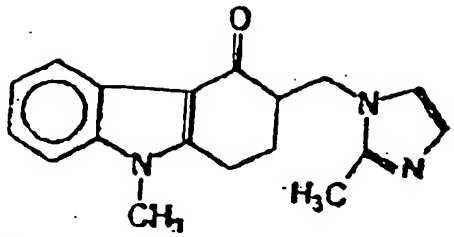
3位氢酸性不够强，但在Lewis酸类催化剂作用下，通过Lewis酸负离子中心电荷向醛胺缩合的亚胺正离子的部份转移，例如经可能的中间体结构式（XI），促进了亚胺正离子中间体（XII）的生成，化学结构式（Ⅳ）的烯醇式中间体化合物（XIII）与亚胺中间体（XII）的加成完成通式（Ⅱ）



(XI)



(XII)



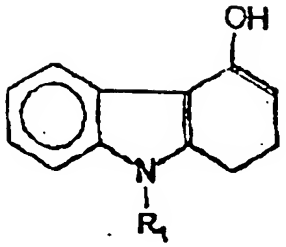
(II)

根据本发明制备的该有机碱及其合格的生理盐和溶剂化物作为选择性5—羟基色胺（5-HT_3）受体的拮抗剂是强有效的．现在称为5-HT_3受体包括称为5-HT_3，5-HT_3M'或5-HT_3 'M－式' 受体，过去对这类受体已有较详细的描述．例如在下述若干论文中：Fozard, et al Eur. J. pharmacol., 1979. 59, 195～210; Irelard, Straughan, Typers, Brit. J. pharmacol., 1982, 75 16p; Humphrey, Neuropharm 1984, 23, 1503～1570; Richardson et al, Nature 1985, 316, 126～131; Bradlay et al, Neuropharm 1986, 25, 563～576．已发现许多化合物是5-HT_3受体的有效拮抗剂，它们通常是氮杂双环衍生物，苯甲酸衍生物或咪唑衍生物，在下列专利中揭示了这些化合物的化学结构式；它们是美国专利：2100259 2125398 2131420 2132189 2145416 2152049 2153821和2169292．欧洲专利：111608 116255 158265 191562 210840 — 214772 219103 221702 226267 227215 230718 235878 242973 225545 220011 275669．澳大利亚专利：8767121．德国公开专利：3740352．日本公开特许：昭61-212521，昭62-77380，昭62-77381．中国专利申请号85105643．

本项研究旨在发明批量生产恩丹西酮及其合格生理盐的新方法，提供有实用价值和经济效益的生产工艺．

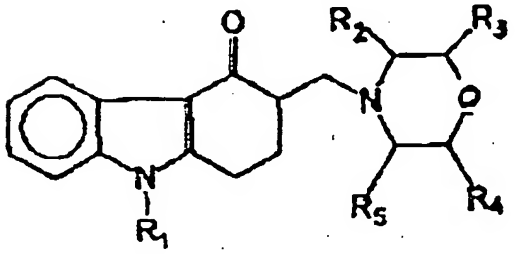
按照本专利提供的制备通式（Ⅰ）化合物的第一种方法（A），通式为（Ⅱ）的化合物或含量大于30％的混合物被选择性

化合物的制备，在结构式（XIII）中R_1表示$C_1 \sim C_6$的直链或脂环状烷基.

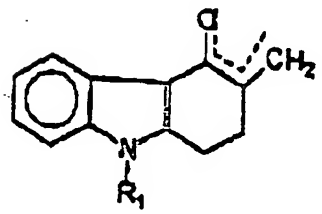


(XIII)

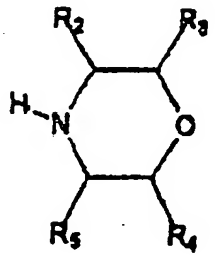
按照本专利提供制备通式（II）化合物的制备方法（C），在含水的质子型混合溶剂中，化学结构式（III）化合物在Lewis酸催化下迅速解离成可能结构式为（XIV）的不稳定中间体和化学结构式为（VII）的杂环胺分子，化学结构式中：R_1表示$C_1 \sim C_6$的直链或脂环状烷基；R_2、R_3、R_4、R_5表示$C_1 \sim C_3$的短链正烷基或异烷基.



(III)



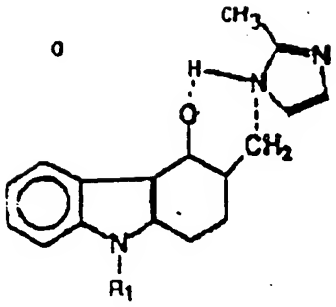
(XIV)



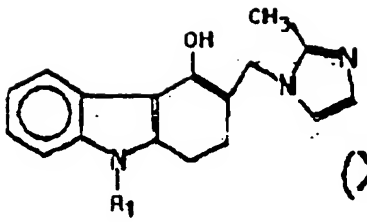
(VII)

中间体（XIV）经2-甲基咪唑的1，4加成中间过渡态（XVI），首先生成化学结构式（XVII）的化合物，（XVII）的C_3，C_4间的双键处于顺式位置，因此，立即转化成能量上较稳定的反式位置，也即（XVII）的酮式结构，该酮式结构就是结构式为

（Ⅱ）的化合物.

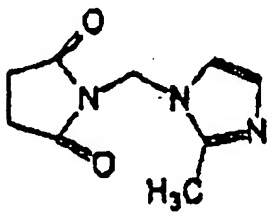


(XVI)



(XVII)

按照本专利提供的制备化学结构式（Ⅱ）的制备方法（D），在酸性的质子型溶剂中化学结构式（Ⅳ）化合物和化学结构式（Ⅴ）或（Ⅵ）的化合物在加温条件下（如25～100℃）发生



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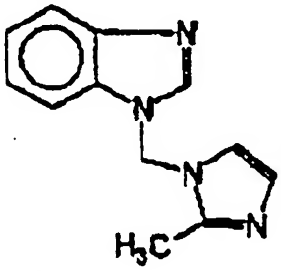
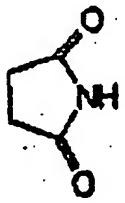
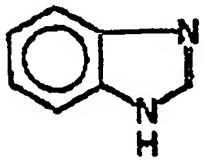


(VI)

酮交换反应，反应结束后，可以分离得到琥珀酰亚胺（XVIII）或苯骈咪唑（XIX），所以，该交换反应的第一步极可能是



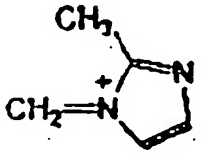
(XVIII)



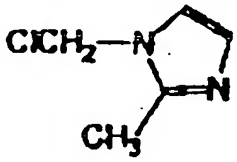
(XIX)

（Ⅴ）或（Ⅵ）发生质子诱导的分解反应，除生成（XVIII）或（XIX）外，还生成重要的亚胺正离子中间体（XII）和（Ⅳ）立即发生加成反应而生成化学结构式（Ⅱ）的化合物．在实施制备方法（D）时，反应中间体不需要分离纯化，即是一锅法合成．在制备

方法（D）中需要的（V）或（VI）从易得的N-氯甲基-2-甲基咪唑（XX）分别和琥珀亚胺或苯骈咪唑加热反应而得.

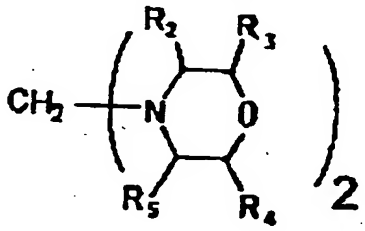


(XII)



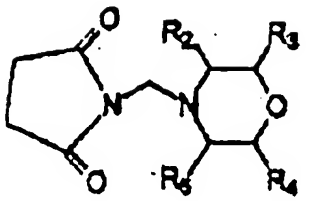
(XX)

按照本专利提供的制备化学结构式（III）化合物的制备方法（F），卟唑-4-酮（IV），多聚甲醛和结构式（VII）化合物的催化缩合反应，为加快反应，反应中用如$AgNO_3$，$Cu_2X_2(X=Cl,Br,I)$，$Cu(OAc)_2$，Al_2O_3等固体Lewis酸催化剂或它们的混合型复合催化剂或盐酸等无机酸，实施制备方法（F）时，可以是三种组份同时加入，也可以先不加入（IV）和酸，让多聚甲醛和结构式（VII）的胺类化合物，先发生醛胺缩合反应，该缩合反应只可能生成醛胺分子比例为1：2的缩合物（XXI），（XXI）同样可和（IV）在酸性条件下反应生成结构式（III）化合物.

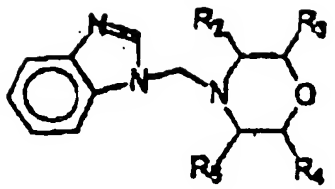


(XXI)

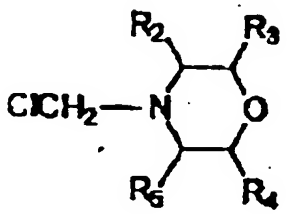
按照本专利提供的制备结构式（III）化合物的制备方法（G），化学结构式（IV）化合物和化学结构式（VIII）或（IX）化合物的酮反应，交换反应最好在加温条件下进行（例如30～150℃），而制备方法（G）中所用的化学结构式（VIII）或（IX）化合物分别由化学结构式化合物（XXII）与琥珀酰亚胺（XVIII）或苯骈咪唑（XIX）加热反应而得.



(VIII)



(XI)



(XXII)

结构式中：R_2、R_3、R_4、R_5表示$C_1 \sim C_3$的短链正烷基或异烷基或氢原子.

按照本专利制备的恩丹西酮及众多的中间体中，特别要提到1,1,2,2,3－五氢-9－甲基-3-〔（吗啡啉基-N）-甲基〕-4-氧代咔唑，1,1,2,2,3-五氢-9-甲基-3-〔（2′,6′-二甲基-吗啡啉基-N）-甲基〕-4-氧代咔唑，上述二种咔唑的化学结构由^1HNMR、IR、MS、$^{13}CNMR$和元素分析结果确认. $-CH_2CH_2CH-$的化学位移在1.80～3.00 ppm,9位$N-CH_3$的特征性单峰化学位移在3.68 ppm，3位的次甲基桥氢在^1HNMR谱上发现出二个双峰，在谱图上还出现吗啡啉部的特征性谱图，在质谱图上，除出现预计的分子离子峰外，M/Z198（$M^+\text{-}CH_2\text{-}N$⟨⟩O）是上述二种咔唑的共同基峰. 在IR谱图上，除羰基的1640cm^{-1}峰外，还普遍有1580，1480cm^{-1}的苯环峰. 1,1,2,2,3-五氢-9-甲基-3-〔（2′-甲基咪唑-1）甲基〕-4-氧代咔唑及它与硅胶复合物的结构差别证明在红外光谱上，复合物的苯环基的特征吸收光谱分别位移30～40cm^{-1}说明该复合物是层迭的平板

状结构，该咔唑是作为负电荷中心，不饱和键与氧化硅的空穴间形成氢键，保证了酸和溶剂分子从另一面向咔唑分子的进攻。

本专利涉及到经过新颖反应中间体化合物合成恩丹西酮及其合格生理盐的新方法，反映中间体是经光谱技术和元素分析确认结构的新化合物，具有原料易得，反应条件温和，操作简便，产物易于提纯的优点。

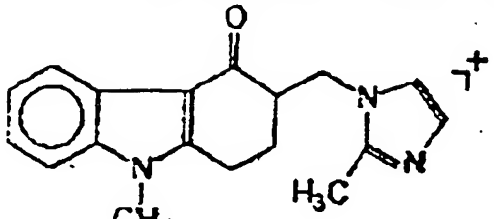
下面的例子说明本发明在经已知化合物校正过的毛细管测定熔点，红外、氢核磁谱和质谱分别在Simadzu IR-440型、Bruker AM 300型和HP 5989A型光谱仪上测定。

实例A_1:

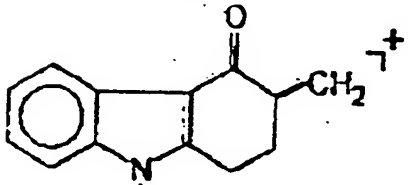
盐酸1,1,2,2,3-五氢-9-甲基-3〔（2′-甲基咪唑-1-基）甲基〕-4-氧代咔唑二水化合物（X）及一水化合物。

由5g（0.017mol）实例C，D或E制备的化合物（Ⅱ）和50ml乙酸乙酯混合加热，使成小颗粒的悬浮液，趁热加入装有薄层层析硅胶柱中，柱直径5cm，柱长15cm，通入少量N_2气压力，先用300ml乙酸乙酯洗脱，收集之洗脱液蒸去乙酸乙酯，残留100mg黄色粘液，薄板层析检测为前沿杂质，继而用200ml乙酸乙酯洗脱收集液浓缩，残留物为白色固体，检测为实例F，G制备化合物（Ⅲ），即回收原料0.8g，然后用1N HCl水溶液洗脱，继而用1000ml水洗脱，水溶液合并浓缩，冷却，结晶，抽滤，结晶物在红外上干燥，得4.75g标题化合物（X），产率90.54%，mp. 176～178℃，分析样品，用水重结晶一次，并在具有P_2O_5干燥器中真空干燥，得到一水化合物，元素分析：$C_{18}H_{19}N_3O\cdot HCl\cdot H_2O$，MW，347.83，实测值（计算值）%：C 62.44（62.16），H 6.12（6.38），N 12.12

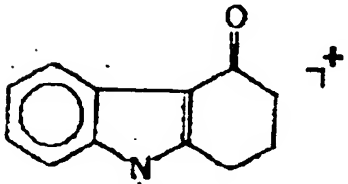
(12.08), Cl 10.46 (10.19); IR: υ_{max} 3200-3400 (OH), 1630 (C=C), 1620 (C=O), 1580, 1480, 760cm^{-1}, MS: M/Z,



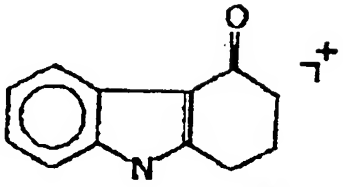
293 ( ),



211 ( ),



198 ( ), 183 (



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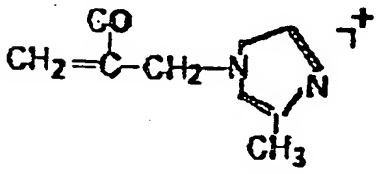
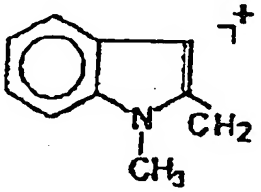


149 ( ), 143 (



),

55 ($H_2C{-}CHC{\equiv}O^{+}$); $^{1}HNMR$: $DMSO-d_6$, δ_{1H}, 1.90~2.25, 2.96~3.25, (5H, m, $-CH_2-CH_2-CH-$), 2.65 (3H, S, $C-CH_3$), 3.74 (3H, S, $N-CH_3$), 4.23~4.31, 4.63~4.69 (2H, dd-dd, $-CH_2-$), 7.55~7.69 (2H, d, d CH=CH), 7.19~7.29, 7.50~7.55 (3H, m, ArH), 7.97~8.05 (1H, m, ArH); $^{13}CNMR$: δ_{13C}, 191.18, 152.83, 144.44, 137.41, 124.05, 122.65, 122.26, 122.20, 122.01, 117.71, 110.60, 110.26, 46.87, 45.36, 29.76, 26.20, 20.64, 10.42.

实例A_2:

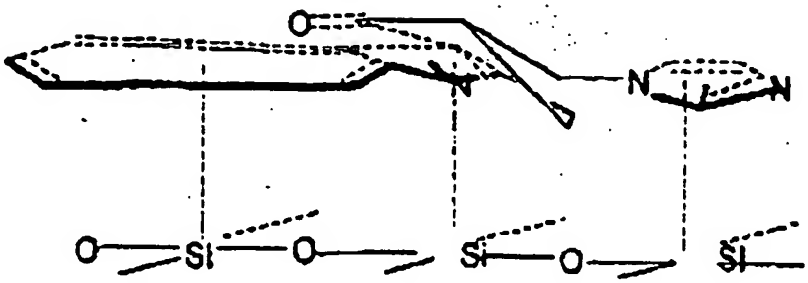
盐酸1,1,2,2,3-五氢-9-甲基-3-〔(2′-甲基咪唑-1-基)甲基〕-4-氧代咔唑二水化合物(X)及一水化合物.

由5g(0.017mol)实例C, D或E制备的化合物(Ⅱ)悬浮于40ml乙醇中, 加入30g氢型阳离子交换树脂, 搅拌半小时后, 悬浮物消失, 继续搅拌半小时, 滤出树脂, 并用乙醇洗涤, 抽干树脂, 放回到烧杯中, 加入40ml 0.1N HCl,搅拌1~2小时, 滤出酸液, 树脂中再加入新鲜40ml 0.1N HCl搅拌, 如此反复操作多次, 滤出酸液合并, 浓缩, 冷却, 结晶, 滤出, 干燥, 得4.5g标题化合物(X), 产率72.05%, mp. 176~178℃, 放入具P_2O_5干燥器中真空干燥, 得一水化合物, 元素分析: $C_{18}H_{19}N_3O\cdot HCl\cdot H_2O$, MW, 374.83, 实测值(计算值)%: C 62.46(62.16), H 6.24(6.12), N 12.04(12.07), Cl 10.41(10.19); IR、MS、^1HNMR、$^{13}CNMR$光谱与实例A_1产物相同.

实例A_3:

10mg1,1,2,2,3-五氢-9-甲基-3〔(2′-甲基咪唑-1-基)甲基〕-4-氧代咔唑溶解于5ml乙酸乙脂中在薄层硅胶板上作薄板层析, 用5~10%乙酸乙脂—正已烷作梯次展开剂, 手提式紫外灯检测试剂的展开状况, 用双光束反射式NICOLET IR光谱仪, 测定红外光谱, 发现原归属为C=C的吸收峰从1630cm^{-1}位移到1675cm^{-1}处, 而原归属为C=O吸收峰仅从1620cm^{-1}位移到1625cm^{-1}处, 表明该氧代咔唑在硅胶上呈重叠式吸附, 分子间氢键由C=C双键作电子结体和硅胶的空穴作电子受体而形成, 而C_4位的C=O键则不与吲哚环和咪唑环在同一平面上, 故C=O键的位移值极小, 1,1,2,2,3-五氢-9-甲基

-3-〔（2′-甲基咪唑-1- 基）甲基〕-4-氧代咔唑在SiO_2表面上呈如下结构:



HYPETCHEM 三型量化计算表明分子的π体系取共平面，羰基位于平面外，二个甲基也位于平面外的构型，分子可获得3.214千焦耳/摩尔的稳定能，而从双键的红外位移值计算（$E=h\upsilon$）分子π电子和SiO_2空穴间的作用能为0.5382千焦耳/摩尔.

实例B:

盐酸1,1,2,2,3-五氢-9-甲基-3-〔（2′-甲基咪唑-1-基）甲基〕-4-氧代咔唑二水化合物（X）

实例C，D或E制备的化合物（Ⅱ），用甲醇重结晶2次，干燥后，取0.25g（0.85mmol）（Ⅱ）溶于5ml乙醇中，通入干HCl气体，待pH3时，停止，冷却，结晶，过滤出固体，用水重结晶，得220mg白色标题化合物（X），产率70.45%，mp. 176~178℃，IR、MS、^1HNMR、$^{13}CNMR$光谱与实例A_1产物相同.

实例C:

1,1,2,2,3-五氢-9-甲基-3-〔（2′-甲基咪唑-1-基）甲基〕-4-氧代咔唑（Ⅱ）

实例C_1:

2.5g 2-甲基咪唑溶于20ml乙醇中，在水浴中冷却，加入等当量的浓H_2SO_4搅拌，除去冰浴，加入2.98g（10mmol）实例F或G制备的化合物（III），90℃左右，搅拌5小时，蒸去大部分乙醇溶剂，冷却，加入100ml水，析出固体，抽滤，滤并用水洗涤，干燥，得2.5g标题化合物（II），mp. 220～223℃，含量85%，分析样品：用甲醇重结晶，干燥，得2.2g白色粉状物，mp. 227～228℃，产率75.1%，元素分析：$C_{18}H_{19}N_3O$，MW，293.35，实测值（计算值）%：C 73.45（73.70），H 6.54（6.53），N 14.01（14.32）；IR、MS测定结果与实例C_2相同；^1HNMR：$CDCl_3$，δ_{1H} 1.80～1.94，2.04～2.25，2.82～3.02（5H，m，$-CH_2-CH_2CH-$），2.46（3H，S，$C-CH_3$），3.68（3H，S，NCH_3），4.07～4.14，4.62～4.69（2H，dd-dd，$-CH_2-$），6.91～6.95（2H，d-d，CH=CH），7.31～7.33（3H，m，ArH），8.22～8.26（1H，m，ArH）。

实例C_2:

在250ml三口瓶中，加入3克（0.01mol）1,1,2,2,3-五氢-9-甲基-3〔（吗啡啉基-N-）甲基〕-4-氧代咔唑，用3N盐酸调节至pH6，然后，加入40ml正丙醇及5克（0.06mol）2-甲基咪唑，搅拌至反应物溶解，在95℃下加热35小时，冷却，滤出固体，在甲醇中脱色和重结晶，得到2.62克白色粉末状固体，mp. 227～228℃，产率85.9%，元素分析$C_{18}H_{19}N_3O$，MW，293.35，实验值（计算值）%：C 73.45（73.72），H 6.54（6.58），N 14.01（14.22）；IR：υ_{max} 3050，2920，2850，1630，1620，1580，1480，1280，

1200. 760cm^{-1}; MS: M/Z 293 (M^+), 211, 198, 183, 149, 144, 55; $\delta_{1H}(CDCl_3)$ 8.23~8.26 (1H, m, ArH), 7.33~7.31 (3H, m, ArH), 6.95~6.91 (2H, dd, CH=CH), 4.69~4.62, 4.14~4.07 (2H, dd, dd, $-CH_2-$), 3.68 (3H, S, NCH_3), 2.46 (3H, S, $C-CH_3$), 3.02~2.82, 2.25~2.04, 1.94~1.80 (5H, m, $-CH_2-CH_2CH-$) ppm.

实例C_3:

实验步骤类似于实例C_2，不同之处仅在于加料次序，游离和卡唑曼尼希碱和2-甲基咪唑先溶解于正丙醇中，再用3N盐酸调节反应混合物至pH6，在95℃下加热35小时后，按实例C_2方法纯化产物，胺交换产率达81.3%.

实例C_4:

在250ml三口瓶中加入7.1克（0.06mol）2-甲基咪唑盐酸盐，3克（0.01mol）1,1,2,2,3-五氢-9-甲基-3-〔（吗啡啉基-N-）甲基〕-4-氧代卡唑和40ml正丙醇，用3N盐酸调节反应混合物至pH6，在95℃下加热35小时，随后按例实C_2方法作后处理，得到2.35克标题化合物，产率77.01%.

实例D_1:

1,1,2,2,3-五氢-9-甲基-3-〔（2′-甲基咪唑-1-基）甲基-4-氧代卡唑（II）.

14.85g（0.15mol）琥珀酰亚胺和15ml二甲基甲酰胺溶液滴

加入由13克（0.1mol）N-氯甲基-2-甲基咪唑，10.6克（0.1mol）碳酸钠和50ml二甲基甲酰胺组成的反应混合物中，滴加时保持反应温度为60℃，滴加完后，慢慢升温至100℃，保持此温度搅拌2小时，冷却，倾入到1000ml冰水中，有机相用苯提取3×15ml，提取液和有机相合并，水洗至中性，蒸去溶剂，得到粗产品15.9克，产率92%，产物不经纯化就用于下一步反应。

2.0g（10mol）化合物（IV），2.0g（10.4mmol）N-（2′-甲基咪唑-1-基）甲基—琥珀酰亚胺溶于25ml乙醇中，用2N HCl调节pH6，加热回流，搅拌10小时，冷却，加入100ml 1N HCl，滤出固体不溶物，水相用苯提取，苯层水洗，分出水，用无水硫酸钠干燥，并蒸去苯回收化合物（IV）0.8g，水相碱化用Na_2CO_3，析出固体，抽滤，滤并水洗，干燥，得标题化合物1.2g mp. 220～223℃，产率68.26%。

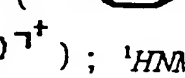
实例E:

1,1,2,2,3-五氢-9-甲基-3-〔（2′-甲基咪唑-1-基）甲基〕-4-氧代咔唑（II）

2.0g（10mmol）化合物（IV），1.2g（40mmol）多聚甲醛，1.6g（19.5mmol）2-甲基咪唑及40ml乙醇搅拌混合，再加入Cu_2Cl_2-HCl催化剂，加热回流，搅拌20小时，冷却，50ml 1N HCl搅拌，不溶物滤出，水相用苯提取3×3ml，苯层合并，用水洗，然后用无水硫酸钠碱化，析出固体，冷却，抽滤，滤出固体水洗，干燥，得0.85g粗产物，mp. 218～222℃用甲醇重结晶，干燥，得0.26g克产物，产率8.87%，mp. 228～229℃，IR、MS、^1HNMR同于实例C制备化合物。

实例F:

1,1,2,2,3-五氢-9-甲基-3-〔（吗啡啉-N-基）甲基〕-4-氢代咔唑（Ⅱ）

2.0g（10mmol）化合物（Ⅳ），1.2g（40mmol）多聚甲醛，1.74g（20mmol）吗啡啉溶于20ml乙酸中，搅拌，加热70℃下反应5小时，冷却，加入50ml 1N HCl，搅拌，滤出不溶物，水相用苯提取3×3ml，苯层合并，用水洗涤，苯层用无水硫酸钠干燥，蒸去苯，残留物0.2g，为回收的（Ⅳ）。水相与洗涤水合并，用固体*NaOH*碱化，析出固体，冷却，抽滤，滤并用水洗，干燥，得2.2g标题化合物（Ⅱ），产率81.21%，分析样品：用乙酸乙酯重结晶，得白色晶体，mp. 165.5~166.5℃，元素分析：$C_{18}H_{22}N_2O_2$，MW，298.37，实测值（计算值）%：C 71.94（72.46），H 7.53（7.43），N 9.28（9.38）；IR：υ_{max} 1640，1620，1580，1480，760cm^{-1}；MS：M/Z，299（$M^+ + 1$），298（M^+），211（  ），198（），183，100（）；^1HNMR：$CDCl_3$，δ_{1H}，8.23（1H，m，ArH），7.26~7.30（3H，m，ArH），3.70~3.78（4H，m，CH_2OCH_2），3.86（3H，S，$N-CH_3$），2.20~3.06（11H，m，CH_2NCH_2，CH_2CH_2CH,CH_2）。

实例G:

1,1,2,2,3-五氢-9-甲基-3-〔（吗啡啉-N-基）甲基〕-4-氧代咔唑（Ⅲ）

14.85g（0.15mol）琥珀酰亚胺和15ml二甲基甲酰胺溶液滴加入由13克（0.1mol）N-氯甲基-2-甲基咪唑10.6克（0.1mol）碳酸

钠和50ml二甲基甲酰胺组成的反应混合物中，滴加时保持反应温度为60℃，滴加完后，慢慢升温至100℃，保持此温度搅拌2小时，冷却，倾入到1000ml冰水中，有机相用苯提取3×15ml，提取液和有机相合并，水洗至中性，蒸去溶剂，得到粗产品15.9克，产率92%，产物不经纯化就用于下一步反应。

2.0g（10mmol）化合物（IV），2.0gN-（吗啡啉-N-基）甲基-琥珀酰亚胺溶于乙醇中，用2N HCl调节pH6，加热回流20小时，蒸去乙醇，加入50ml 1N HCl，搅拌溶解，滤出不溶物，滤液用苯提取，苯层合并，用水洗，无水硫酸钠干燥，蒸去苯，残留物显黄色固体，0.5g检测为回收的化合物（IV），水相用*NaOH*碱化，析出固体，过滤，滤并水洗，干燥，得1.2g标题化合物，产率53.69%，分析样品用乙酸乙酯重结晶，mp. 165.5~166.5℃，IR、MS、^{1}*HNMR*光谱数据同实例F制得化合物一致。

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CY=CN DATE=19951213 KIND=A
PN=1,113,234

SYNTHESIS OF ONDANSETRON AND ITS PHYSIOLOGICAL SALT
[Endanxitong Ji Qi Shengliyande Hecheng]

Wu Guosheng, et al.

UNITED STATES PATENT AND TRADEMARK OFFICE
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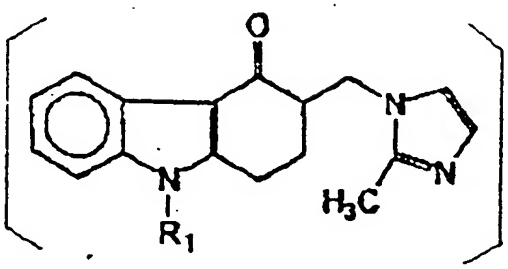
Claims

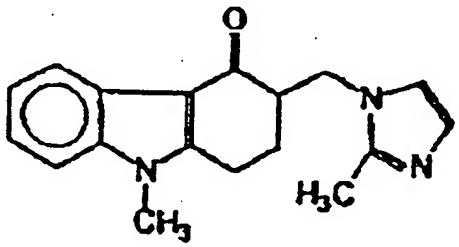
1. Method of preparing general formula (I)



A·S (I)

In this structural formula, A designates hydrochloric acid, sulfuric acid, hydrobromic acid, oxalic acid, maleic acid, organic acid or inorganic acid; S designates an aqueous solvent; R_1 designates a C_1 ~ C_6 straight chain or alicyclic alkyl radical; the preparation method of the general formula (I) includes:

(A) a salt-forming reaction on the solid/liquid interface between the compound of general formula (II) or its protected derivative or a reaction mixture that makes up more than 30% and A;



(II)

(B)a salt-forming reaction on the liquid/gas interface between the compound of general formula (II) or its protected derivative or

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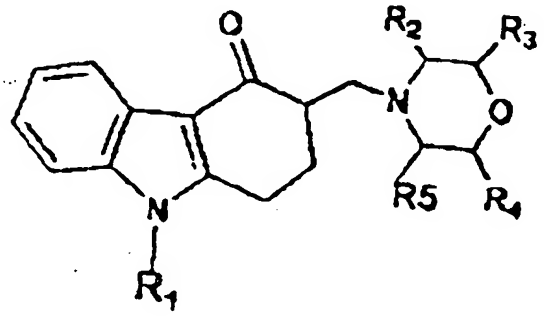
*Number in the margin indicates pagination in the foreign text.

a reaction mixture where it makes up more than 30% and A;

2. Method of preparing the general formula (II) described in Claim 1:

(C) An exchange reaction between the compound of general formula (III) and 2-methylimidazole or other amines;

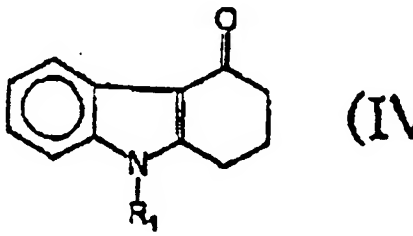


(III)

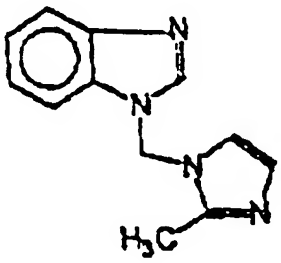
/3

In this structural formula, R_1 designates a C_1 ~ C_3 short chain normal alkyl or isoalkyl radical, or hydrogen atoms, while R_2, R_3, R_4, R_5 can designate identical or different substituting groups or substituting groups may be absent;

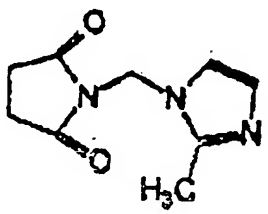
(D) Ketone exchange reaction between the compound of chemical structural formula (IV) and the compound of chemical structural formula (V) or (VI);



(IV)



(VI)



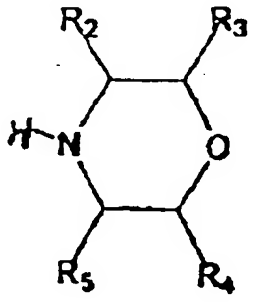
(V)

In this structural formula, R_1 designates a $C_1 \sim C_6$ straight chain or alicyclic alkyl radical;

(E) a catalytic condensation reaction of the compound of chemical structural formula (IV), paraformaldehyde and 2-methyl imidazole, the solid catalyst used in this reaction is $AgNO_3$, $Cu_2X_2(X=C_1, Br, I)$, $Cu(OAc)_2$, Al_2O_3, Lewis acid, or a mixed or composite catalyst made up therefrom.

3. Method of preparing the chemical structural formula (III) described in Claim 2 that includes:

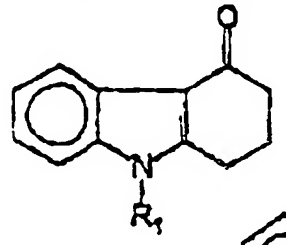
(F) a catalytic condensation reaction of the compound of /4 chemical structural formula (IV), paraformaldehyde and the compound of chemical formula (VII), the solid catalysts used in this reaction are $AgNO_3$, $Cu_2X_2(X=C_1, Br, I)$, $Cu(OAc)_2$, Al_2O_3, Lewis acid, or a mixed or composite catalyst made up therefrom or hydrochloric acid, sulfuric acid, or inorganic acids;



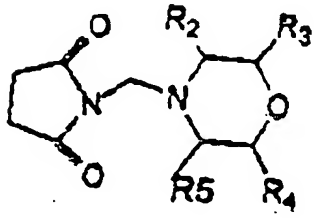
(VII)

In the structural formula, R_2, R_3, R_4, R_5 designate $C_1 \sim C_3$ short chain normal alkyl or isoalkyl or hydrogen atoms;

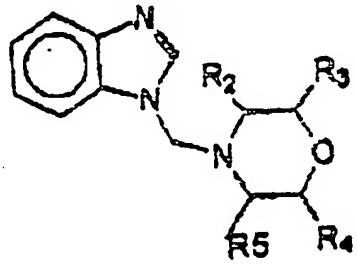
(G) Ketone exchange reaction between the compound of chemical structural formula (IV) and the compound of chemical structural formula (VIII) or (IX);



(IV)



(VIII)



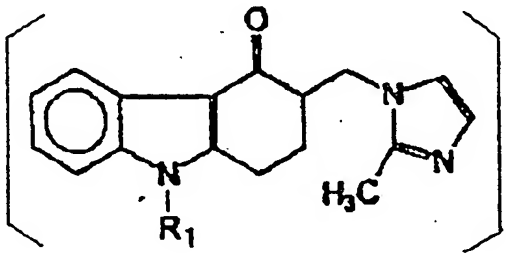
(IX)

In this structural formula, R_1 designates a $C_1 \sim C_6$ straight chain or alicyclic alkyl radical, while R_2, R_3, R_4, R_5 designate $C_1 \sim C_3$ short chain normal alkyl or isoalkyl or hydrogen atoms.

4. Among the numerous important intermediate products of ondansetron hydrochloride prepared in accordance with one of the Claims 1~3, the most useful compound is the complex of 1, 1, 2, 2, 3 - pentahydro-9-methyl-3-[(2'-methylimidazole-1)-methyl]-4-oxocarbazole and silicon dioxide or ion exchange resin. /5

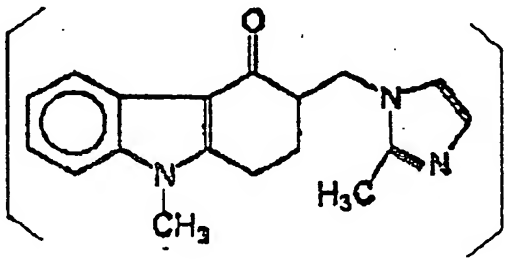
Synthesis of Ondans tron and its Physiological Salt

This invention pertains to the preparation of an organic base used as medication and its standard physiological salt and solvate. The general formula of the chemical structure of this compound is expressed by formula (I):



A·S (I)

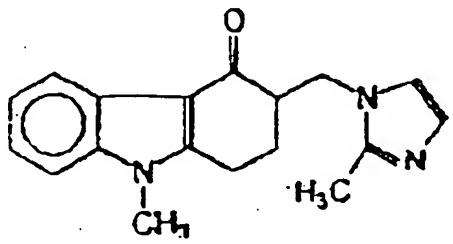
In this structural formula, **A** designates hydrochloric acid, sulfuric acid, hydrobromic acid, oxalic acid, maleic acid, organic acid or inorganic acid; **S** designates an aqueous solvent; R_1 designates a $C_1 \sim C_6$ straight chain or alicyclic alkyl radical; its hydrochloride dihydrate (X) is used as medication under the conventional trade name of Ondansetron hydrochloride.



$HCl \cdot 2H_2O$ (X)

Its chemical name is 1, 1, 2, 2, 3 - pentahydro-9-methyl-3-[(2'-methylimidazole-1)-methyl]-4-oxocarbazole, and its structural formula is expressed as (II):

/7



(II)

The organic base and its standard physiological salt and solvate prepared in accordance with this invention is an effective blocking agent of the 5- hydroxy tryptamine (5-HT_3) receptor type. What is currently referred to as 5-HT_3 receptors includes the 'M-type' receptors 5-HT_3, 5-HT_3M' or 5-HT_3, receptors of this type were successfully described in the past. For example, in the following several articles [Fozard, et al, Eur. J. Pharmacol., 1979.59, 195 ~ 210; Irelard, Straughan, Typers, Brit. J. Pharmacol., 1982, 75 16p; Humphrey, Neuropharm 1984, 23, 1503 ~ 1570; Richardson et al,Nature 1985, 316, 126 - 131; Bradlay, et al, Neuropharm 1986, 25, 563 ~ 576. Numerous effective 5-HT_3 receptor blocking agents had been previously discovered, usually they were azadicyclo- derivatives, benzoic acid derivatives or imidazole derivatives; chemical structural formulas of these compounds were disclosed in the following patents: US patents 2100259, 2125398, 2131420, 2132189, 2145416, 2152049, 2153821 and 2169292; European patents 111608,

116255, 158265, 191562, 210840, 214772, 219103, 221702, 226267, 227215, 230718, 235878, 242973, 225545, 220011, 275669; Australian patent 8767121; German PUBLIC Patent 3740352; Japanese Kokai patent Sho61-212521, Sho 62-77380, Sho 62-77381; Chinese patent application 85105643.

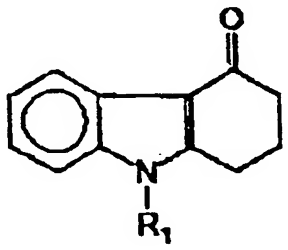
The gist of this research is the discovery of a new method for the batch manufacturing of Ondansetron and its standard physiological salt, and the offering of a practically valuable and economically efficient manufacturing process.

According to the first method (A) suggested in this patent for the preparation of the of compound of general formula (I), due to a selective interaction between the compound of general formula (II) or a mixture containing more than 30% thereof and an organic acid or inorganic acid solution of appropriate concentration on supports /8 made of weak acid type ion exchange resin or silicic acid G (≤ 100 mesh)or Caprone powder or diatomite or cationic alumina, a reaction occurs on the solid/liquid interface, and the compound of general formula (I) is obtained with high selectivity.

According to method (B) suggested in this patent for the preparation of the of compound of general formula (I), by continuously adding the compound of general formula (II) or a mixture containing more than 30% thereof to a water/alcohol solvent while at the same time continuously adding hydrogen chloride and other gases, the compound of general formula (I) can be obtained

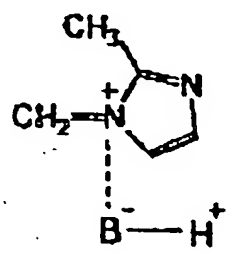
continuously.

According to method (E) suggested in this patent for the preparation of compound (II), the compound of chemical structural formula (IV) is an aromatic ketone compound, 2-methyl imidazole is an aromatic amine compound, and under the regular Mannich reaction conditions, they primarily enter into an amine-aldehyde condensation reaction, generating a resin-type polycondensate. Moreover, the acidity of hydrogen in the 3rd place of the compound of general formula (IV) that falls under aromatic ketones.

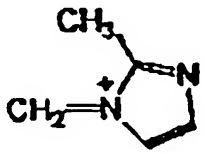


(IV)

is not strong enough, however, under the effect of the Lewis acid catalyst, due to the partial shift of the central charge of the Lewis acid anions to the imine cations of the amine-aldehyde condensation, it facilitated , for example, the generation of the imine cation intermediate (XII) through the possible intermediate structural formula (XI). By adding the enol type intermediate compound (XIII) of the chemical structural formula (IV) to the imine intermediate (XII) the preparation of the preparation of the compound of general formula (II)

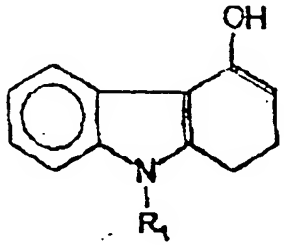


(XI)



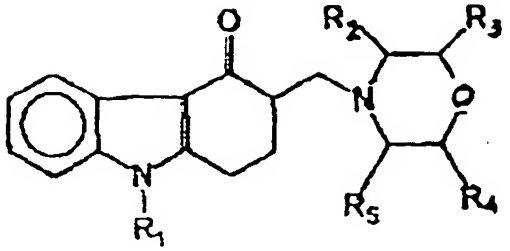
(XII)

is completed. In the structural formula (XIII) R_1 designates a /9 $C_1 \sim C_6$ straight chain or alicyclic alkyl radical.

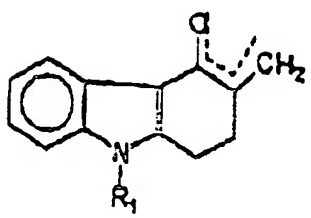


(XIII)

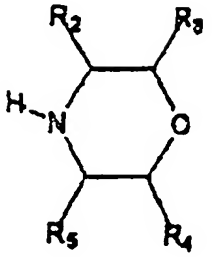
According to method (C) suggested in this patent for the preparation of the of compound of general formula (II), in an aqueous protonic mixed solvent, a compound of chemical structural formula (III), with a Lewis acid as a catalyst, quickly dissociates into an unstable intermediate with a possible structural formula (XIV) and molecules of heterocyclic amines of structural formula (VII); in this chemical structural formula R_1 designates a $C_1 \sim C_6$ straight chain or alicyclic alkyl radical, while R_2, R_3, R_4, R_5 designate $C_1 \sim C_3$ short chain normal alkyls or isoalkyls.



(III)

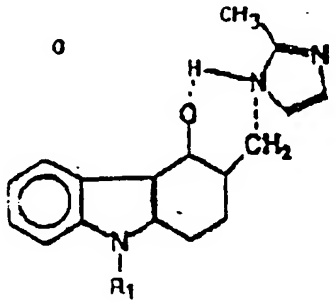


(XIV)

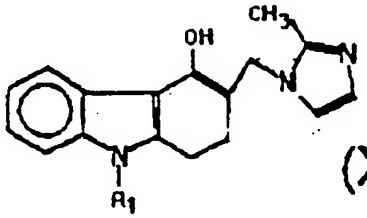


(VII)

The intermediate compound (XIV) forms an intermediate transition complex (XVI) by adding 2-methylimidazol at 1 and 4. First, a compound with a chemical structural formula (XVII) is formed; the double bond between C_3 and C_4 in (XVII)is in the *cis*-position. Therefore it immediately converts into an energetically more stable *trans*-position, which is also the ketone type structure of (XVII). This ketone type structure is in fact the compound with structural formula (II). /10



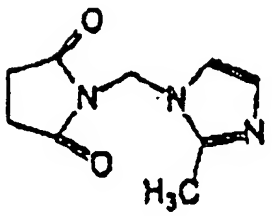
(XVI)



(XVII)

According to method (D) suggested in this patent for the preparation of the of compound of chemical structural formula (II), in an acidic protonic solvent, at elevated temperatures (e.g.,

25~100°C), a compound of chemical structural formula (IV)and compounds of chemical structural formulas (V) and (VI) engage



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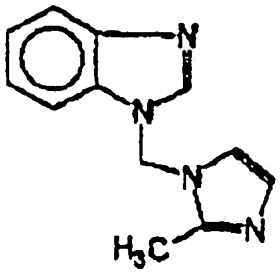
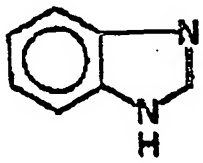


(VI)

in an exchange reaction, and upon its completion, succinimide (XVIII) or benzimidazole (XIX), therefore the first step of this exchange reaction quite possibly is

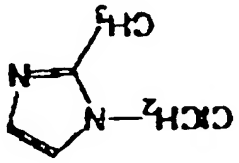
(XVIII)

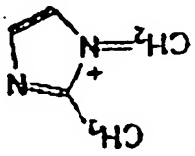


(XIX)

(V) or (VI) start a proton-induced decomposition reaction, and apart from producing (XVIII) or (XIX), they also produce the important imide cation intermediate (XII) and (IV) immediately enters an addition reaction generating compounds of chemical structural formula (II). When method (D) is implemented, the reaction intermediates do not require separation or purification; /11 rather, they are produced by a "single kettle" method. (V) or (VI) required for the preparation method (D)are obtained by the addition

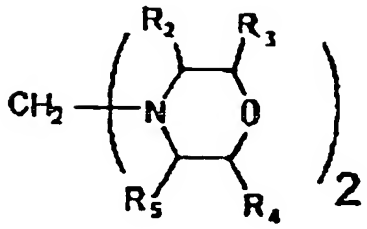
and heating reaction between the easily obtainable N-chloromethyl-2-methylimidazole (XX) and suucinimide or benzimidazole, respectively,

(XX) 

(IIX) 

According to method (F) suggested in this patent for the preparation of the compound of chemical structural formula (III), in a catalytic condensation reaction of carbazo-4-ketone (IV), paraformaldehyde and a compound with structural formula (VII), to accelerate the reaction, solid Lewis acid catalysts such as $AgNO_3$, Cu_2X_2 (X=Cl, Br, I), $Cu(OAc)_2$, Al_2O_3 etc., or mixed type complex catalysts or hydrochloric acid and other inorganic acids are used in the reaction. When implementing the preparation method (F)the three kinds of components can be added simultaneously , or we can first refrain from adding (IV) and acids, allowing the parafomaldehyde and amine compounds to engage in the amine-aldehyde condensation reaction. The amine-aldehyde condensation reaction can only produce condensate (XXI) with aldehyde to amine molecule ratio of 1:2. (XXI) can similarly produce a compound of structural

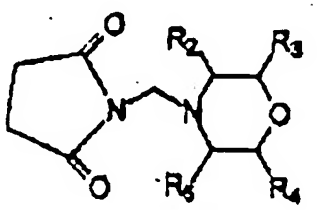
formula (III) in a reaction with (IV) under acidic conditions.



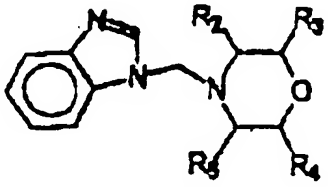
(XXI)

According to method (G) suggested in this patent for the preparation of the compound of chemical structural formula (III), the ketone reaction and exchange reaction of the compound of chemical structural formula (IV) and compound of chemical structural formula (VIII) or (IX) is best carried out under elevated temperature (30-150°C). Compounds of structural chemical formulas (VIII) or (IX) utilized in the preparation method (G)ar obtained by heating reactions the compound of chemical structural formula (XXII) and succinimide or benzimidazole, respectively.

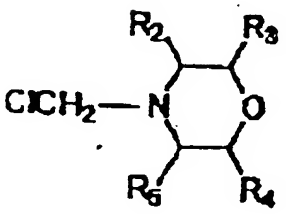
/12



(VIII)



(XI)



(XXII)

In this structural formula, R_2, R_3, R_4, R_5 designate C_1 ~ C_3 short chain normal alkyls or isoalkyls or hydrogen atoms.

Among the ondarsetron and its numerous intermediates prepared according to this invention, especially worth mentioning are 1, 1, 2, 2, 3 - pentahydro-9-methyl-3-[(morpholine group-N)-methyl]-4-oxocarbazole and 1, 1, 2, 2, 3 - pentahydro-9-methyl-3-[(2', 6'-dimethyl-morpholine group-N)-methyl]-4-oxocarbazole . Chemical structures of the above-mentioned two types of carbazole were confirmed by the results of ^{1}HNMR, IR, MS, ^{13}CNMR and elemental analysis. The chemical displacement of $-CH_2CH_2CH-$ is at 1.80 ~ 3.00 ppm, the chemical displacement of the characteristic single peak of $N-CH_3$ in position 9 is at 3.68 ppm, while methine epihydro in position 3 revealed itself in two double peaks on the ^{1}HNMR spectrum. The characteristic spectrum of morpholine also showed up. In mass-spectrography apart from the emergence of precalculated molecular and ionic peaks, M/Z198($M^+-CH_2-N\langle\rangle O$) is the shared base peak of the above-mentioned two kinds of carbazole. In the IR spectrum, except for the carbonyl peak at 1640 cm^{-1}, benzene ring peaks at 1580 and 1480 cm^{-1} were also common. 1, 1, 2, 2, 3 - pentahydro-9-methyl-3-[(2'-methylimidazole-1)-methyl]-4-oxocarbazole and its structural difference from the silicagel complex are evidenced in the infrared spectrum. The fact that characteristic absorption spectra of the benzene ring groups in the complex compound are located at 30 ~ 40 cm^{-1} proves that this

complex compound has a layered flat structure with carbazole as the center of negative charge and unsaturated bonds forming hydrogen bonds with the holes of silicon oxide, thus guaranteeing that the acid and solvent molecules attack carbazole molecules on the other side. /13

This invention pertains to a new method for synthesizing ondansetron and a physiological salt thereof through a novel reaction intermediate compound; in reflection of the fact that the intermediate compound has been confirmed by spectrometry and elemental analysis to be a structurally new compound. It is advantageous in that the raw material is easy to obtain, the reaction conditions are mild, the operations are straightforward, and the product is easy to purify.

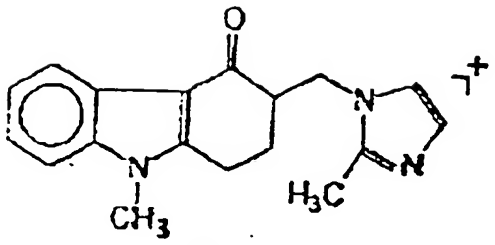
For the examples below we explain that the measuring of the melting point was performed using a capillary tube calibrated with a known compound; that the infrared, hydrogen nuclear magnetic and mas spectra were measured using the spectrometers Simadzu IR-440, Bruker AM 300, and HP 5989A.

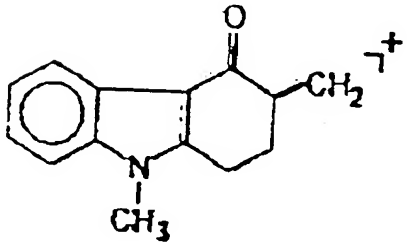
Practical Example A_1:

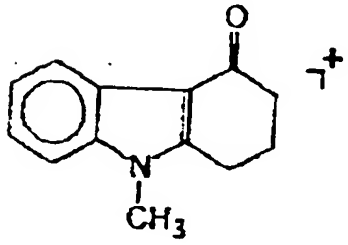
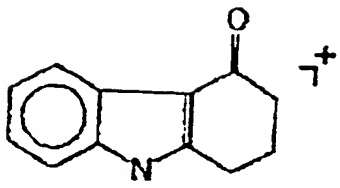
1, 1, 2, 2, 3 - pentahydro-9-methyl-3-[(2'-methylimidazole-1)-methyl]-4-oxocarbazole hydrochloride dihydrate compound (X) and monohydrate compound.

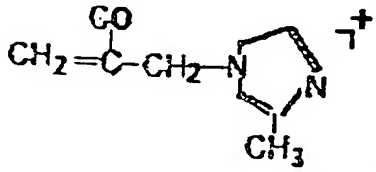
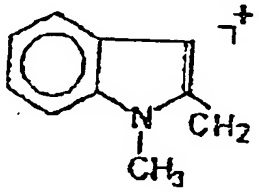
A mixture of 5 g (0.017 mol) of compound (II) prepared in Practical Examples C, D or E with 50 ml of ethyl acetate was heated

to form a suspension of small particles; while hot it was placed in a silica gel column for thin layer analysis, the column diameter was 5 cm, the column length was 15 cm. The pressure of a small amount of N_2 gas was applied and elution performed with 300 ml of ethyl acetate; ethyl acetate was then removed by evaporation the collected eluate obtained by; the residue consisted of 100 mg of yellow sticky liquid. It was examined by thin layer chromatography to bring forward impurities, then the liquid obtained by elution with 200 ml of ethyl acetate was condensed. The residue was a white solid, it was determined as the compound (III) prepared per Practical Examples F and G. 0.8 g of raw material was recovered and then eluted with 1N water solution of HCl with subsequent elution with 1000 ml of water. The water solutions were jointly condensed, cooled, crystallized, filtered, and the crystals dried in infrared light. 4.75 g of the title compound (X) was obtained, the yield was 90.54%m mp was 176 ~ 178°C. The analyzed samples were recrystallized with water and vacuum-dried in a drier containing P_2O_5. A monohydrate compound was obtained, its elemental analysis is $C_{18}H_{19}N_3O \cdot HCl \cdot H_2O$, MW 347.83. The actually measured values (calculated values) in %: C 62.44(62.16), H 6.12 (6.38), N 12.12 (12.08), Cl 10.46 (10.19); IR: υ_{max} 3200-3400 (OH), 1630 (C=C), 1620 (C=O), 1580, 1480, 760cm^{-1}, MS: M/Z,

293 (),

211 (),

198 (), 183 (),

149 (), 143 (),

55 (H_2C–CHC≡O$^+$); ^1HNMR:DMSO-d_6, δ_{1H}, 1.90~2.25, 2.96~3.25, (5H, m, $-CH_2-CH_2-CH-$), 2.65 (3H, S, $C-CH_3$), 3.74 (3H, S, $N-CH_3$), 4.23~4.31, 4.63~4.69 (2H, dd-dd, $-CH_2-$), 7.55~7.69 (2H, d, d CH=CH), 7.19~7.29, 7.50~7.55 (3H, m, ArH), 7.97~8.05 (1H, m, ArH); $^{13}CNMR$:δ_{13C}, 191.18, 152.83, 144.44, 137.41, 124.05, 122.65, 122.26, 122.20, 122.01, 117.71, 110.60, 110.26, 46.87, 45.36, 29.76, 26.20, 20.64, 10.42.

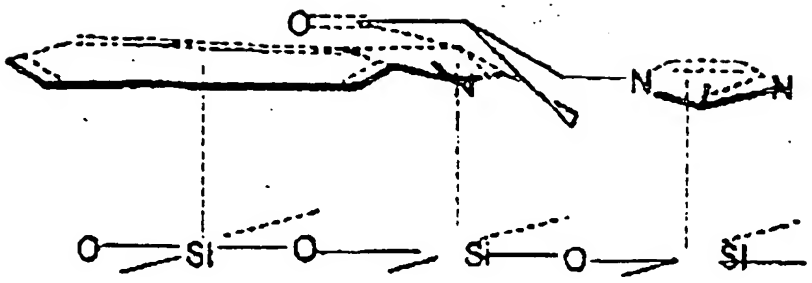
Practical Example A_2:

1, 1, 2, 2, 3 - pentahydro-9-methyl-3-[(2'-methylimidazole-1)-methyl]-4-oxocarbazole hydrochloride dihydrate compound (X) and monohydrate compound.

5 g (0.017 mol) of compound (II) prepared in Practical Examples C, D, or E was suspended in 40 ml of ethanol, to which was added 30 g of hydrogen type ion exchange resin and stirred for half an hour, whereupon the suspended matter disappeared but the stirring continued for another half hour. The resin was filtered out and rinsed with ethanol. After blow drying the resin was placed back into the Bunsen beaker and, upon adding 40 ml of 0.1N HCl, the contents were stirred for 1 ~ 2 hrs. Acid liquor was filtered out, another 40 ml of fresh 0.1N HCl was added to the resin and stirred. This operation was repeated many times. The filtered acid liquor was combined, condensed, cooled down, crystallized, filtered and dried to obtain 4.5 g of the title compound (X). The yield was 72.05%, mp. 176 ~ 178°. The compound was vacuum-dried in a drier containing P_2O_5. A monohydrate compound was obtained, its elemental analysis is $C_{18}H_{19}N_3O \cdot HCl \cdot H_2O$, MW 374.83. The actually measured values (calculated values) in %: C 62.46(62.16), H 6.24 (6.12), N 12.04 (12.07), Cl 10.41 (10.19); the IR, MS, ^{1}HNMR and ^{13}CNMR spectra were the same as those of the product in the Practical Example A_1.

Practical Example A_3:

10 mg of 1, 1, 2, 2, 3 - pentahydro-9-methyl-3-[(2'-methylimidazole-1)-methyl]-4-oxocarbazole was dissolved in 5 ml of ethyl acetate and thin layer chromatography was performed on a thin layer silica gel plate, and with 5 ~ 10% of ethyl acetate - n-hexane as a tiered developing agent, the reagent's developing status was detected with a portable ultraviolet lamp. Using the double beam reflection type spectrometer NICOLET IR, the IR spectrum was determined, and it was discovered that the absorption peak originally attributed to C=C moved from 1630 cm^{-1} to 1675 cm^{-1},while the absorption peak originally attributed to C=O only moved from 1620 cm^{-1} to 1625 cm^{-1}, which showed that this oxacarbazole demonstrates overlapping adsorption on silica gel, and intermolecular hydrogen bonds are formed by the C=C double bonds as the electron donors and silica gel holes as the electron recipient. The C_4 C=O bond, on the other hand is not on the same plane as the indole ring or the imidazole ring, therefore the shift value of C=O bond is very small. 1, 1, 2, 2, 3 - pentahydro-9-methyl-3-[(2'-methylimidazole-1)-methyl]-4-oxocarbazole displays the following /16 structure on the surface of SiO_2.



Quantum chemistry calculations by HYPETCHEM-3 show a configuration where the molecules' π system takes a co-plane, while the carbonyl group is positioned outside the plane and the two methyl groups also are positioned outside the plane. Molecules can receive 3.214 KJ/mole of stabilizing energy, and when calculated from double bond infrared shift value ($E=h\nu$) the energy of interaction between the π electrons of molecules and the holes of SiO_2 is 0.5382 KJ/mole.

Practical Example B:

1, 1, 2, 2, 3 - pentahydro-9-methyl-3-[(2'-methylimidazole-1)-methyl]-4-oxocarbazole hydrochloride dihydrate (X)

Compound (II) prepared in the Practical Examples C, D or E was twice recrystallized with methanol and dried, whereupon 0.25 g (0.85 mmol) of (II) was dissolved in 5 ml of ethanol, and dry gaseous HCl was blown in until such time when pH was 3 when it was stopped. Cooling down, crystallization and filtering produced a solid which was recrystallized with water to obtain 220 mg of white title substance (X). The yield was 70.45%, mp was 176 ~178°, while

the IR, MS, ^{1}HNMR and ^{13}CNMR spectra were the same as those of the product in the Practical Example A_1.

Practical Example C:

1, 1, 2, 2, 3 - pentahydro-9-methyl-3-[(2'-methylimidazole-1)-methyl]-4-oxocarbazole (II)

Practical Example C_1: /17

2.5 g of 2-methyl imidazole were dissolved in 20 ml of ethanol, cooled down in a water bath, and an equivalent amount of H_2SO_4 was added thereto and stirred. The ice bath was removed and 2.98 g (10mmol) of compound (III) prepared in Practical Examples F or G added to the mixture. After stirring for 5 hours at around 90°C, most of ethanol solvent evaporated. After cooling down and adding 100 ml of water, a solid substance precipitated, it was filtered and the filter cake rinsed with water and dried. 2.5 g of the title compound (II) was obtained, mp. 220 ~ 223°C, content 85%. Analytical sample: recrystallized with methanol and dried, 2.2 g of white powder was obtained, mp. 227 ~ 228°C, yield 75.1%, elementary analysis $C_{18}H_{19}N_3O$, MW 293.35, The actually measured values (calculated values) in %: C 73.45(73.70), H 6.54 (6.53), N 14.01 (14.32), the IR and MS, measurement results were the same as those of the product in the Practical Example C_2.

^1HNMR: $CDCl_3$, δ_{1H}

1.80 ~ 1.94, 2.04 ~ 2.25, 2.82 ~ 3.02 (5H, m, $-CH_2-CH_2CH-$), 2.46 (3H, S, $C-CH_3$), 3.68 (3H, S, NCH_3), 4.07 ~ 4.14, 4.62 ~ 4.69 (2H, dd-dd, $-CH_2-$), 6.91 ~ 6.95 (2H, d-d, CH=CH), 7.31 ~ 7.33 (3H, m, ArH), 8.22 ~ 8.26 (1H, m, ArH).

Practical Example C_2:

Into a 250 ml three-necked flask was added 3 grams (0.01 mol) of 1, 1, 2, 2, 3 - pentahydro-9-methyl-3-[(morpholine group-N)-methyl]-4-oxocarbazole, and pH was adjusted to 6 by 3N hydrochloric acid. Then were added 40 ml of n-propanol and 5 grams (0.06 mol) of 2-methyl imidazole and stirred till the reaction product was dissolved. After heating at 95°C for 35 hrs, it was cooled, solids were filtered out, decolored and recrystallized in methanol. 2.62 grams of white solid in powder form was obtained, mp. 227 ~ 228°C, yield 85.9%, elementary analysis $C_{18}H_{19}N_3O$, MW 293.35. Experimental values (calculated values) in %: C 73.45 (73.72), H 6.54 (6.58), N 14.01 (14.22);

IR: ν_{max} 3050, 2920, 2850, 1630, 1620, 1580, 1480, 1280, 1200. 760cm^{-1}; MS: M/Z 293 (M^+), 211, 198, 183, 149, 144, 55; $\delta_{1H}(CDCl_3)$ 8.23~8.26 (1H, m, ArH), 7.33~7.31 (3H, m, ArH), 6.95~6.91 (2H, dd, CH=CH), 4.69~4.62, 4.14~4.07 (2H, dd, dd, $-CH_2-$), 3.68 (3H, S, NCH_3), 2.46 (3H, S, $C-CH_3$), 3.02~2.82, 2.25~2.04, 1.94~1.80 (5H, m, $-CH_2-CH_2CH-$) ppm. /18

Practical Example C_3:

The experimental procedure was similar to that of the Practical Example C_2. The difference only lies in the order of feeding. Free carbazole, Mannich base and 2-methylimidazole were first dissolved in n-propanol and then pH of the reaction mixture was adjusted to 6 with 3N hydrochloric acid. After heating for 35 hours at 95°C, the product was purified by the method of Practical Example C_2. The amine exchange yield was 81.3%.

Practical Example C_4:

A 250 ml three-necked flask was filled with 7.1 grams (0.06 mol) of 2-methyl imidazole hydrochloride, 3 grams (0.01 mol) of 1, 1, 2, 2, 3 - pentahydro-9-methyl-3-[(morpholine group-N)-methyl]-4-oxocarbazole and 40 ml of n-propanol. The reaction mixture pH was adjusted to 6 with 3N hydrochloric acid. 35 hours of heating at 95°C were followed by post-treatment by the method of Practical Example C_2. 2.35 g of the title compound was obtained with a yield of 77.01%.

Practical Example D_1:

1, 1, 2, 2, 3 - pentahydro-9-methyl-3-[(2'-methylimidazole-1)-methyl]-4-oxocarbazole (II)

14.85 g (0.15 mol) of succinimide and of 15 ml of a dimethyl formamide solution were added by dropping into a reaction mix that /19 consisted of 13 grams (0.1 mol) of N-chloromethyl-2- methyl imidazole, 10.6 grams (0.1 mol) of sodium carbonate and 50 ml of dimethyl formamide, over the course of dropping the temperature was maintained at 60°C and upon completion it was slowly raised to 100°C. While maintaining this temperature the mixture was stirred for 2 hours, cooled and placed into 1000 ml of ice water. The organic phase was extracted with benzene 3x 15 ml. The extract was combined with the organic phase, rinsed with water to neutrality, and the solvent was evaporated. 15.9 grams of crude product was obtained with a yield of 92%. The product was used in the reaction of the next step without purification.

2.0 g (10 mol) of compound (IV) and 2.0 grams (10.4 mmol) of N-(2'-methyl imidazole-1) methyl succinimide were dissolved in 25 ml of ethanol, and pH was adjusted to 6 with 2N HCl. The solution was heated, refluxed, stirred for 10 hours and cooled. 100 ml of 1N HCl were added thereto and solid substance was filtered off. We extracted the water phase with benzene, rinsed the benzene layer with water, separated the water and used anhydrous sodium sulfate for drying. Upon benzene evaporation 0.8 g of product (IV) was

recovered, Na_2CO_3 was used to basify the water phase. The solids were precipitated, filtered, the filter cake was rinsed with water, dried, and 1.2 g of title compound was obtained, mp.220 ~ 223°C, with a yield of 68.26%.

Practical Example E:

1, 1, 2, 2, 3 - pentahydro-9-methyl-3-[(2'-methylimidazole-1)-methyl]-4-oxocarbazole (II)

2.0 g (10 mmol) of compound (IV), 1.2 g (40 mmol) of paraformaldehyde, 1.6 g (19.5 mmol) of 2-methyl imidazole and 40 ml of ethanol were stirred and mixed. Cu_2Cl_2 - HCl catalyst was added thereto, which was followed by heating and refluxing, stirring for 20 hours, cooling, stirring in of 50 ml 1N HCl, and filtering off the insoluble matter. The water phase was extracted with benzene 3 x 3ml, the benzene layers were combined, rinsed with water, basified with anhydrous sodium sulfate. The solid matter was precipitated, cooled, filtered, and the filtered solids were rinsed with water and dried to obtain 0.85 g of crude product, mp. 218 ~ 222°C, which was recrystallized with methanol and dried to obtain 0.26 g of the product, with a yield of 218 ~ 229°C; IR, MS and ^{1}HNMR were the same as in the product prepared in the Practical Example C.

Practical Example F:

1, 1, 2, 2, 3 - pentahydro-9-methyl-3-[(morpholine group-N)-methyl]-4-oxocarbazole (II)

2.0 g (10 mmol) of compound (IV), 1.2 g (40 mmol) of paraformaldehyde, and 1.74 g (20 mmol) of morpholine were dissolved in 20 ml of acetic acid, stirred; and after heating to 70°C the reaction ran for 5 hours. This was followed by cooling, adding 50 ml of 1N HCl, stirring, filtering off the insoluble matter, and extracting the water phase with benzene 3x3ml. The benzene layers were combined, rinsed with water, dried with anhydrous sodium sulfate, and benzene was evaporated. 0.2 g of residue was the recovered (IV). The water phase was combined with the rinse water and basified with solid NaOH. The solid matter was precipitated, cooled, filtered, and on rinsing the filter cake with water and drying, 2.2 g of the title compound (II) was obtained, with a yield of 81.21%. Analytical sample: was recrystallized with ethyl acetate, white crystals were obtained, mp. 165.5 ~ 166.5°C. Elementary analysis: $C_{18}H_{22}N_2O_2$, MW 298.37, the actual measured values (calculated values) in %: C 71.94 (72.46), H 7.53 (7.43), N 9.28 (9.38); IR: υ_{max} 1640, 1620, 1580, 1480, 760cm^{-1}; MS: M/Z, 299 ($M^+ + 1$), 298 (M^+), 211 (), 198 (), 183, 100 (); ^1HNMR: $CDCl_3$, δ_{1H}, 8.23 (1H, m, ArH), 7.26 ~ 7.30 (3H, m, ArH), 3.70 ~ 3.78 (4H, m, CH_2OCH_2), 3.86 (3H, S, $N-CH_3$), 2.20 ~ 3.06 (11H, m, CH_2NCH_2, CH_2CH_2CH,CH_2).

Practical Example G:

1, 1, 2, 2, 3 - pentahydro-9-methyl-3-[(morpholine group-N)-methyl]-4-oxocarbazole (III)

A solution of 14.85 g (0.15 mol) of succinimide and 15 ml of dimethylformamide was added by dropping into a reaction mixture made up of 13 g(0.1 mol) of N-chloromethyl-2-methyl imidazole, 10.6 g of sodium carbonate and 50 ml of dimethylformamide. Over the /21 course of dropping the temperature was maintained at 60°C and upon completion it was slowly raised to 100°C. While maintaining this temperature the mixture was stirred for 2 hours, cooled and placed into 1000 ml of ice water. The organic phase was extracted with benzene 3x 15 ml. The extract was combined with the organic phase, rinsed with water to neutrality, and the solvent was evaporated. 15.9 grams of crude product was obtained with a yield of 92%. The product was used in the reaction of the next step without purification.

2.0 g (10 mmol) of compound (IV), 2.0 g of N-(morpholine-N-)-methyl succinimide were dissolved in ethanol, pH was adjusted to 6 with 2N HCl. The solution was heated and refluxed for 20 hours, ethanol was evaporated, and 50 ml of 1N HCl was added and stirred to dissolve. Upon filtering the insoluble matter, the filtrate was extracted with benzene, the benzene layers were combined, rinsed with water and dried with anhydrous sodium sulfate. Benzene was evaporated and the residue was a solid of clear yellow color.).5

g were detected to be recovered compound (IV). The water phase was basified with NaOH, solid matter was precipitated, filtered, and the filter cake was rinsed with water and dried to obtain 1.2 g of the title compound, with a yield of 53.69%. The analytical sample was recrystallized with ethyl acetate, mp. 165.5 ~ 166.5°C, IR, MS and ^{1}HNMR spectral data converge with those of the compound obtained in the Practical Example F.